FORMULARY REVIEW

Inhaled anesthetic agents

JOAN STACHNIK

Purpose. The pharmacology, bioavailability and pharmacokinetics, indications, clinical efficacy, adverse effects and toxicities, and dosage and administration of the inhaled anesthetics are reviewed.

Summary. The inhaled anesthetics include desflurane, enflurane, halothane, isoflurane, and sevoflurane and are thought to enhance inhibitory postsynaptic channel activity and inhibit excitatory synaptic activity. The mechanism of action of inhaled anesthetics has not been completely defined. A number of factors can influence the pharmacokinetics of inhaled anesthetics, including solubility in blood, cardiac output, tissue equilibration, extent of tissue perfusion, metabolism, and age. All of the available inhaled anesthetics are effective for inducing or maintaining anesthesia or both. Most clinical trials of inhaled anesthetics have evaluated differences in induction and emergence from anesthesia by comparing (1) times to loss of reflex, extubation, and response to verbal commands; orientation to time and place; and ability to sit up without assistance, (2) need for postsurgical analgesia, and (3) time to discharge as measures of efficacy. Adverse effects and toxicities of the inhaled anesthetics include nephrotoxicity, hepatotoxicity, cardiac arrhythmias, neurotoxicity, postoperative nausea and vomiting, respiratory depression and irritation, malignant hyperthermia, and postanesthesia agitation. Safety issues surrounding these gases include occupational exposure and intraoperative fires within the delivery systems used with inhaled anesthetics. Drugs used for anesthesia during surgery can account for 5–13% of a hospital's drug budget.

Conclusion. The inhaled anesthetics have been shown to be both safe and effective in inducing and maintaining anesthesia. These agents differ in potency, adverse-effect profile, and cost. Newer anesthetic gases, such as sevoflurane and desflurane, appear to have more favorable physicochemical properties. These factors, as well as patient characteristics and duration and type of procedure, must be considered when selecting an inhaled anesthetic.

Index terms: Age; Anesthetics; Costs; Desflurane; Dosage; Drug administration; Drugs; Drugs, availability; Drugs, body distribution; Enflurane; Halothane; Health professions; Inhalers; Isoflurane; Mechanism of action; Metabolism; Patients; Pharmacokinetics; Sevoflurane; Solubility; Surgery; Tissue levels; Toxicity, environmental; Toxicity

Am J Health-Syst Pharm. 2006; 63:623-34

The use of inhaled anesthetics began in the mid-1800s, when it was discovered that the inhalation of diethyl ether relieved pain.[1-3] Despite the adverse effects associated with ether (e.g., unpleasant taste, prolonged recovery time, nausea, vomiting), the agent remained the preferred anesthetic for nearly 100 years. Advances in fluorine chemistry after World War II allowed for the development of halogenated compounds, which are more stable and potent and less toxic than diethyl ether. In 1956, halothane, a fluorinated alkane, was introduced and quickly replaced ether as the anesthetic of choice. Other agents, halogenated compounds with ether linkages, followed: enflurane in 1972, isoflurane in 1981, desflurane in 1992, and sevoflurane in 1995.

Currently, desflurane, isoflurane, and sevoflurane constitute the primary inhaled anesthetic gases used either alone or in combination with nitrous oxide, with or without concurrent administration of other drugs such as midazolam, propofol,

JOAN STACHNIK, PHARM.D., BCPS, is Clinical Assistant Professor, Department of Pharmacy Practice, College of Pharmacy, University of Illinois Medical Center at Chicago, Chicago, IL.

Address correspondence to Mary Ellen Bonk, Pharm.D., University HealthSystem Consortium, 2001 Spring Road, Suite 700, Oak Brook, IL 60523-0890 (bonk@uhc.edu).

The University HealthSystem Consortium acknowledges Eric L. Chernin, B.S.Pharm., Scott M. Eleff, M.D., Julie Golembiewski, Pharm.D., and Deborah Wagner, Pharm.D., for their review of this monograph.

DOI 10.2146/ajhp050460

The Formulary Review *section contains monographs provided to* AJHP *by the Clinical Knowledge Service, Drug Monograph Group, of the University HealthSystem Consortium (UHC), Oak Brook, IL. The monographs are written by drug information specialists and pharmacotherapists from UHC member institutions and VHA institutions, undergo peer review by UHC and VHA pharmacists and physicians, and appear here some months after initial distribution. They have been edited by* AJHP *and contain new abstracts. For more information, see the initial installment in the December 1, 1997, issue or call Karl A. Matuszewski, M.S., Pharm.D., or Mary Ellen Bonk, Pharm.D., at UHC (630-954-1700).*

thiopental, fentanyl, and various muscle relaxants. This review focuses on the efficacy and use of desflurane, enflurane, halothane, isoflurane, and sevoflurane.

Pharmacology

The mechanism of action of inhaled anesthetics has not been completely defined. Early research suggested a relationship between potency and lipophilicity (defined as solubility in olive oil), with the anesthetic effect resulting from a nonspecific effect on hydrophobic cellular components.[4,5] However, subsequent research focused on the molecular targets of anesthetics, specifically ion-channel activity. Certain ion channels have been shown to be sensitive to inhaled anesthetics when administered at clinically effective concentrations.[4] These ion channels include neurotransmitter receptors (e.g., γ-aminobutyric acid type A, glycine, nicotinic acetylcholine, serotonin, and glutamate receptors) and voltage- and non-voltage-activated calcium, sodium, and potassium channels. Inhaled anesthetics are thought to enhance inhibitory postsynaptic channel activity and inhibit excitatory synaptic activity.[4,5] The proposed actions of the anesthetic gases on ion channels are summarized in Table 1. However, additional mechanisms may be responsible for the actions of some inhaled anesthetics, since nitrous oxide, an effective nonhalogenated anesthetic, appears to have little to no effect on most ion channels.

One aspect of the pharmacology of inhaled anesthetics is their potency, which is based on the alveolar concentrations that result in clinical effects.[3,4] Potency, as well as dosage, is expressed as the minimum alveolar concentration (MAC) and is defined as the alveolar concentration of an anesthetic needed to prevent a response (e.g., movement) to a surgical incision or similar stimulus in 50% of patients at 1 atmosphere of pressure, which can be considered the 50% effective dose of the anesthetic (ED_{50}).[6]

The MAC of an anesthetic agent influences uptake.[3,4,6] In general, if all other characteristics of an agent are equal, the higher the MAC, the higher the uptake of the anesthetic gas and the less potent the agent. A number of factors can influence the MAC, including age (MAC is reduced as age increases), hematocrit levels, pregnancy, medications, electrolyte status, and presence of hyperthermia or hypothermia.[7] The MAC values of the various inhaled anesthetic gases are listed in Table 2.

Bioavailability and pharmacokinetics

A number of factors can influence the pharmacokinetics of inhaled anesthetics.[8] The solubility of the agent in blood, represented by the blood:gas partition coefficient, is an important determinant of uptake. The blood:gas partition coefficient is the ratio of the concentrations of anesthetic gas in the blood and gas

Table 1.
Effects of Anesthetic Gases on Ion Channels[4,5]

Ion Channel	Behaviorial or Physiological Processes Affected	Effect on Ion-Channel Activity[a]
Ligand-gated ion channels—inhibitory postsynaptic receptors		
$GABA_A$[b] receptors	Increased activity results in anxiolysis, sedation, amnesia, myorelaxation, and anticonvulsant activity	Enhancement
Glycine receptors	Inhibitory receptor for spinal reflexes and startle responses	Enhancement
Ligand-gated ion channels—excitatory synaptic receptors		
Neuronal nicotinic acetylcholine receptors	Memory, nociception, autonomic functions	Inhibition
Serotonin type 3 receptors	Arousal, emesis	Inhibition (weak)
Glutamate receptors	Perception, memory, learning, nociception	Inhibition
Other ion channels		
Voltage-activated potassium channels	Nerve conduction, cardiac action potentials	Inhibition or no effect
Voltage-activated sodium channels	Nerve conduction, cardiac action potentials	Inhibition (weak)
Voltage-activated calcium channels	Cardiac inotropy and chronotropy, vascular tone	Inhibition (weak)

[a]Describes actions of halogenated alkanes and ethers.
[b]$GABA_A$ = γ-aminobutyric acid type A.

phases at equilibrium (Table 2). In general, the blood:gas partition coefficient represents the capacity of the blood or a specific tissue to absorb the anesthetic.[1] A higher blood:gas partition coefficient (e.g., 2.0 equals a 2% blood concentration and a 1% lung concentration at equilibrium) shows greater affinity for the blood. The lower the partition coefficient, the lower the affinity of the blood or tissue for the anesthetic.[3] An anesthetic that has a blood concentration of 3% and a lung concentration of 6% at equilibrium would have a partition coefficient of 0.5, showing a greater affinity for the gas phase. In other words, agents with a lower blood:gas coefficient are more rapidly absorbed and excreted, producing a faster onset and shorter duration of action.

After loading of the agent, equilibrium occurs and uptake is reduced, decreasing the amount of anesthetic that needs to be administered.

Other factors that influence the uptake of inhaled anesthetics include cardiac output, tissue equilibration, extent of tissue perfusion (e.g., muscle versus fat tissues), metabolism, and age.[1] Desflurane, isoflurane, and nitrous oxide undergo minimal metabolism. The metabolism of enflurane and sevoflurane is considered intermediate, and halothane is extensively metabolized. The route of elimination for anesthetic gases is via the lungs.

Indications

The labeled indications for the inhaled anesthetics are listed in Table 3.

Clinical efficacy

General anesthesia can be divided into three stages: induction, maintenance, and emergence. All of the available inhaled anesthetics are effective for inducing or maintaining anesthesia or both. Inhaled anesthetics are often used for induction in patients who fear placement of an intravenous access line.[1] For maintenance, it is generally accepted that a MAC of about 1.3 is needed to prevent movement in 95% of patients.[12] Emergence, or awakening from anesthesia, occurs when the MAC drops to 0.3 or 0.4.

Most clinical trials of inhaled anesthetics have evaluated differences in induction and emergence from anesthesia by comparing (1) times to loss of reflex, extubation, and response to verbal commands; orientation to time and place; and ability to sit up without assistance, (2) need for postsurgical analgesia, and (3) time to discharge as measures of efficacy. Recent trials and their results are summarized in Table 4. Both ambulatory care and inpatient adult and pediatric populations are included in the trials.

Adverse effects and toxicities

Renal effects. Nephrotoxicity from inhaled anesthetics has been a concern for nearly 40 years, beginning with the recognition of renal toxicity associated with methoxyflurane (Penthrane [Abbott], which was withdrawn from the market in 2000).[31,32] This effect was thought to be dose related and caused by inorganic fluoride formed secondary to metabolism of the agent.[2,31] Using methoxyflurane as a model, a plasma concentration of inorganic fluoride of >50 μmol/L was thought to result in nephrotoxicity after administration of any inhaled anesthetic.[2,33] The production of inorganic fluoride with desflurane, enflurane, halothane, and isoflurane is limited, and these agents are unlikely to cause significant nephrotoxicity in patients with normal renal function.[31] However, although plasma concentrations of inorganic fluoride have been reported to exceed 50 μmol/L after prolonged administration of sevoflu-

Table 2.
Physicochemical Properties of Inhaled Anesthetic Gases[1-4,8]

Agent	Year Introduced	Halogen	MAC (%)[a]	Blood:Gas Partition Coefficient	Extent of Metabolism after Uptake (%)	Presumed Metabolism
Diethyl ether[b]	1844	NA	NA	NA	NA	NA
Nitrous oxide[b]	Early 19th century	NA	104	0.47	NA	NA
Halothane	1956	Fluorine, chlorine, bromine	0.77	2.5	25–45 (to trifluoroacetate)	Oxidative metabolism
Enflurane	1972	Fluorine, chlorine	1.68	1.8	2–5	CYP isoenzymes (including CYP 2E1)
Isoflurane	1981	Fluorine, chlorine	1.15	1.4	0.2 (to trifluoroacetate)	CYP isoenzymes (including CYP 2E1)
Desflurane	1992	Fluorine	6.0	0.42	0.02 (to trifluoroacetate and inorganic fluoride)	CYP isoenzymes
Sevoflurane	1995	Fluorine	2.05	0.69	0.02 (to trifluoroacetate and inorganic fluoride)	CYP isoenzymes

[a]MAC = minimum alveolar concentration, NA = not available, CYP = cytochrome P-450.
[b]Included for comparison.

Table 3.
Labeled Indications for Inhaled Anesthetics[9-11]

Agent	Indication
Desflurane	Induction and maintenance of general anesthesia in adult patients for inpatient and outpatient surgery
Enflurane	Induction and maintenance of general anesthesia
Halothane	Induction and maintenance of general anesthesia
Isoflurane	Induction and maintenance of general anesthesia
Sevoflurane	Induction and maintenance of general anesthesia in adult and pediatric patients for inpatient and outpatient surgery

rane, reports of renal dysfunction after sevoflurane administration in patients are no higher than they are with other inhaled anesthetic agents.[8,31,33,34] It is now thought that intrarenal inorganic fluoride, resulting from renal defluorination, may be responsible for the nephrotoxicity seen with methoxyflurane. Sevoflurane undergoes limited metabolism within the kidneys.

Compound A (fluoromethyl-2,2-difluoro-1-[trifluoromethyl] vinyl ether),[3] a degradation product of sevoflurane resulting from the interaction between sevoflurane and the absorbents used to remove carbon dioxide during administration, has resulted in mild and reversible renal impairment in animal studies.[3,10,31,33] The amount of compound A produced and the theoretical risk of nephrotoxicity may be dose dependent and have a greater potential to occur when sevoflurane is used for prolonged periods or at low flow rates. In clinical trials, administering sevoflurane at a flow rate of 1 L/min resulted in the increased production of compound A as the duration of anesthesia lengthened.[10] For this reason, administering sevoflurane for over 2 MAC hours is not recommended. To date, there are no reports of compound A toxicity in humans.

Kharasch et al.[35] reported on the renal effects of low-flow anesthesia with sevoflurane versus isoflurane in patients undergoing prolonged surgery. A total of 50 adult patients received either sevoflurane or isoflurane, administered at a rate of 0.8–1 L/min, for surgery that was planned to last eight hours or longer. Renal function (i.e., serum creatinine, creatinine clearance, urinary protein and glucose concentrations) was assessed before and after surgery, as were inspired and expired concentrations of compound A. At 24 and 72 hours after surgery, no significant difference in markers of renal function was seen between the two groups. The mean inspired concentration of compound A was 16 ppm, with a reported maximum of 25 ppm. Total compound A exposure was calculated as 165 ppm/hr, with a maximum reported exposure of 428 ppm/hr. The accepted thresholds for compound A nephrotoxicity in animal studies range from 290–340 ppm/hr (in rats) to 800 ppm/hr (in cynomolgus monkeys).[35]

Obata et al.[36] reported similar findings from a study comparing low- and high-flow sevoflurane. A total of 30 adult patients undergoing surgery of long duration (≥10 hours) were randomly assigned to receive sevoflurane at 1 L/min (low flow), sevoflurane at 6–10 L/min (high flow), or isoflurane at 1 L/min (low flow). From preanesthesia to day 5, no reduction in renal function values (i.e., serum creatinine, blood urea nitrogen, and creatinine clearance) was seen with low-flow sevoflurane, and there were no differences in the values between either low- or high-flow sevoflurane and isoflurane. All patients had increases in other markers of renal function (i.e., urinary excretion of glucose, albumin, protein, and *N*-acetyl-beta-D-glucosaminidase) after anesthesia, with no significant difference among the three groups. In the low-flow sevoflurane group, the mean compound A exposure was 277 ppm/hr.

Hepatotoxicity. Inhaled anesthetics have been associated with hepatotoxicity, with the potential for toxicity related to the degree of metabolism, as well as the intermediate and end products of metabolism.[2] This toxicity is thought to be immune mediated, manifesting as severe, potentially fatal hepatitis. Possible factors predisposing patients to hepatitis include previous exposure, obesity, female sex, short intervals between exposures, a history of postoperative jaundice or pyrexia, and a genetic predisposition to hepatitis. Since halothane is metabolized to the greatest degree, it has a higher rate of hepatotoxicity than other agents, with 1 case in 35,000 patients exposed, compared with 1 in 800,000 for enflurane, <1 in 1,000,000 for isoflurane, and <1 in 10,000,000 for desflurane.[2,3]

Although sevoflurane is metabolized to a greater extent than isoflurane or desflurane, it is thought to have a lower potential for hepatotoxicity. Unlike other anesthetic gases, sevoflurane does not have a reactive metabolite in its metabolic pathway, thus reducing the risk of hepatotoxicity.[2] Halothane is also associated with a non-immune-mediated increase in liver enzymes. This effect is more common than the immune-mediated increase (one case in three patients exposed), is usually subclinical, and may occur without previous exposure to the anesthetic.[2]

Cardiovascular effects. Mean arterial pressure, cardiac output, and systemic vascular resistance are generally reduced or unaffected by inhaled anesthetics.[2] Heart rate is also reduced or unchanged with halothane and sevoflurane. Desflurane, like isoflurane, has been reported to cause transient increases in heart rate.[3] Enflurane may also result in increases in heart rate.[2] Cardiac ar-

Table 4.
Clinical Comparisons of Inhaled Anesthetics[a]

Ref.	Patient Population/ Procedure	Anesthesia Regimen[b]	Outcome Measures	Results
Emergence and Recovery—Adult Patients				
13	42 adult females/ laparoscopic tubal ligation	Sevoflurane 1–2% or desflurane 3–6% (both with nitrous oxide 60% in oxygen)	Time to emergence, recovery, and discharge (using DSST and VAS [sedation, energy, confusion, nausea, coordination, and pain] scores, response to verbal commands, and time to sit and walk)	Duration of anesthesia or surgery did not differ between groups. Emergence time (based on eye opening and extubation) with desflurane was shorter than with sevoflurane ($p < 0.05$). No difference was seen in time to response to verbal commands, sitting, walking, or discharge. VAS and DSST scores were also similar. Rates of postoperative nausea or vomiting were similar (33% for sevoflurane and 38% for desflurane).
14	246 adults/ambulatory care surgery	Sevoflurane or isoflurane (both with nitrous oxide 60%)	Time to extubation, emergence, eye opening, command response, and orientation	Duration of anesthesia was longer with isoflurane than with sevoflurane (60 vs. 50 min, $p < 0.05$). Sevoflurane was associated with significantly shorter times to emergence, command response, orientation, and ability to sit up without nausea or dizziness. Times to first postoperative analgesia and discharge were similar for sevoflurane and isoflurane.
15	120 adult females/ laparoscopic tubal ligation	Sevoflurane 0.6–1.75%, desflurane 2–6%, or propofol 50–150 µg/kg (all with nitrous oxide 60%)	Recovery time (opening eyes on oral command), orientation, and time to "home readiness"	Duration of anesthesia and surgery was similar among groups. Both sevoflurane and desflurane were associated with significantly shorter times to awakening, tracheal extubation, and orientation and lower Aldrete scores[c] ($p < 0.05$). No difference was seen in times to "home readiness" or actual discharge.
16	60 adult females/ laparoscopic tubal ligation (outpatient surgery)	Sevoflurane 1–2% or desflurane 3–6% (both with nitrous oxide 66% in oxygen)	Emergence (response to oral commands) and recovery times (using DSST and VAS scores)	No significant differences were seen in time to emergence from anesthesia (measured by time to eye opening, command response, orientation, sitting in bed, standing, and walking). DSST scores were higher with sevoflurane at all time points during recovery, but significance was seen only at 30 min after extubation. VAS scores (for all 3 variables) were also lower with sevoflurane, but no statistical significance was seen at any time point measured. Discharge occurred earlier with sevoflurane than with desflurane (163 vs. 194 min, $p = 0.07$).
17[d,e]	1562 adults (9 randomized trials)	Sevoflurane (0.6–2.5 MAC hr) or isoflurane (0.8–2.7 MAC hr)	Emergence, response to commands, extubation, orientation, first analgesic, discharge from the recovery room	On the basis of pooled data, sevoflurane resulted in shorter emergence times than isoflurane. No difference was seen between groups in time to discharge from the recovery room.
18	100 adults/pulmonary surgery (lobectomy or pneumonectomy)	Sevoflurane, desflurane, or isoflurane (all with nitrous oxide)	Emergence (using response to oral commands for eye opening and hand squeezing) and recovery time (using Aldrete scores and psychomotor/ cognitive function testing)	Desflurane was associated with shorter emergence times than sevoflurane or isoflurane on the basis of time to eye opening (7.2 vs. 13.7 vs. 14.3 min, respectively; $p < 0.0001$) and extubation (8.9 vs. 18.0 vs. 16.2 min, respectively; $p < 0.0001$). Recovery time (based on Aldrete scores) was shorter with desflurane at 5 and 15 min after extubation ($p < 0.05$ and $p < 0.01$, respectively) than with sevoflurane and isoflurane. Cognitive functioning (ability to state name, date of birth, and 3 flowers or cars) was significantly better with desflurane at 5 min ($p < 0.05$). No difference among the 3 agents was seen at 15 min.

Continued on next page

Table 4 (*continued*)

Ref.	Patient Population/ Procedure	Anesthesia Regimen[b]	Outcome Measures	Results
19[f]	72 adult females/breast surgery	Sevoflurane, desflurane, or isoflurane given at 1.3 MAC (all with nitrous oxide in oxygen [2:1])	Time to emergence and recovery (using VAS or NVR [pain], sedation scores, nausea or vomiting, and breathing frequency)	Time to emergence (eyes open) was similar (7.3 vs. 9.7 vs. 7.3 min for desflurane, isoflurane, and sevoflurane, respectively; p = NS). No significant difference among the 3 agents was seen in pain scores in the PACU. Desflurane was associated with the highest rate of nausea and vomiting in the PACU (67%), compared with isoflurane (22%) and sevoflurane (36%) ($p < 0.01$).
20	30 obese adults (BMI > 35 kg/m^2)/laparoscopic gastric banding	Sevoflurane or isoflurane	Time to emergence, extubation, and recovery (response to oral commands [eye opening for emergence and hand squeezing for recovery])	Duration of anesthesia and surgery was similar for the 2 groups. Sevoflurane was associated with significantly shorter times to extubation ($p < 0.05$), emergence ($p < 0.001$), and recovery ($p < 0.001$) than isoflurane.
21	60 adults/intracranial surgery	Sevoflurane or isoflurane given at 0.5–1.0 MAC	Time to emergence, recovery, and discharge (using response to oral commands, extubation, orientation to time and place, and basic neurologic functioning using the GCS score)	Median emergence time was shorter with sevoflurane than with isoflurane (14 vs. 18 min, $p = 0.02$). Other recovery variables for sevoflurane and isoflurane included extubation (16.5 vs. 20.5 min, $p = 0.08$), hand squeezing on command (17.5 vs. 25 min, $p = 0.03$), foot movement on command (17.5 vs. 25.5 min, $p = 0.01$), orientation to name (26 vs. 30 min, $p = 0.10$), and orientation to birth date and location (30 vs. 31 min, $p = 0.20$). Time to discharge did not differ (166 vs. 157 min for sevoflurane and isoflurane, respectively, $p = 0.80$). Sevoflurane was associated with a faster time to reach a GCS score of 10 than isoflurane (20 vs. 25 min, $p = 0.04$). Times to a score of 13 or more were similar (25 vs. 30 min, $p = 0.19$).
22	50 adults (>65 yr)/ nonemergency surgery lasting ≥ 2 hr	Sevoflurane 0.6–1.75% or desflurane 2–6% (both with nitrous oxide 60% in oxygen)	Time to discharge, emergence, and recovery (using DSST and VAS [pain and nausea] scores, response to oral commands, and orientation to place and time)	Duration of anesthesia or surgery did not differ between groups. Time to discharge from the PACU was also similar for sevoflurane and desflurane (71 vs. 56 min, p value not stated). Time to recovery was shorter with desflurane than with sevoflurane on the basis of median time to eye opening, ability to squeeze fingers, extubation, and orientation ($p < 0.05$). No difference was seen in VAS or DSST scores at any time.
23[f]	127 adults/gynecologic, orthopedic, urologic, or general surgery	Sevoflurane 1.85% or desflurane 6% (both with nitrous oxide 50%)	Time to emergence (response to command, orientation, time to discharge, minutes to modified Aldrete score = 13) and airway responses	Times to response to command, orientation, target Aldrete score, and discharge were 4.9, 7.6, 24, and 59 min, respectively, for desflurane. Corresponding times for sevoflurane were 6.7, 9.4, 29, and 56 min, respectively. Significance in favor of desflurane was seen for times to response to command, orientation, and target Aldrete score ($p = 0.01$, 0.05, and 0.05, respectively). No difference was seen in time to discharge. Scores for airway responses (coughing, breath holding, and laryngospasm) were similar.

Continued on next page

Table 4 (*continued*)

Ref.	Patient Population/ Procedure	Anesthesia Regimen[b]	Outcome Measures	Results
Emergence and Recovery—Pediatric Patients				
24	375 pediatric patients/ outpatient surgery (genitourinary, superficial lower abdominal, or plastic or superficial orthopedic surgery)	Sevoflurane maximum 7% or halothane maximum 4.3% (both with nitrous oxide 60% and oxygen 40%)	Time to induction, duration of anesthesia and surgery, and time to emergence and post-surgical analgesia	Duration of anesthesia and surgery was similar for both groups. Total MAC-hr exposure was shorter with sevoflurane ($p < 0.013$). Both induction and emergence times were significantly shorter with sevoflurane than with halothane (induction: 1.3 vs. 1.6 min for halothane, $p < 0.001$; emergence: 12.3 vs. 20 min for halothane, $p < 0.001$). Patients given sevoflurane achieved a modified Aldrete score of ≥8 faster than those given halothane (19 vs. 25 min, $p < 0.001$) and were oriented to name and place faster (22 vs. 30 min, $p < 0.001$). Time to first postsurgical analgesic was not significantly different. No difference was seen in time to suitability for discharge.
25	80 pediatric patients (age 1–7 yr)/adenoidectomy with bilateral myringotomy (outpatient surgery)	Sevoflurane induction and maintenance, halothane induction and sevoflurane maintenance, halothane induction and maintenance, or halothane induction and desflurane maintenance (all with nitrous oxide 60% in oxygen)	Time to emergence, recovery, and discharge (based on Steward scores,[g] pain, agitation, nausea, ability to walk, and time to drink)	Time to discharge was similar for all groups, with no significant differences seen. Maintenance with desflurane resulted in shorter times to emergence and recovery versus maintenance with halothane or sevoflurane ($p < 0.0001$). Desflurane was associated with a higher rate of postoperative excitation. Postoperative pain and nausea occurred at similar rates among all groups.
26[f]	42 pediatric patients (age 2–16 yr)/elective general plastic or maxillofacial surgery lasting >1 hr	Sevoflurane induction and maintenance (2.5–3.0%) or halothane induction and maintenance (0.8–1.15%) (all with nitrous oxide in oxygen)	Time to induction of anesthesia (loss of eyelash reflex) and time to emergence (eye opening to nonpainful stimuli and response to oral commands)	Times to loss of eyelash reflex were 2.3 min for sevoflurane and 3.1 min for halothane ($p = 0.06$). Times to emergence were 13 and 16 min for sevoflurane and halothane, respectively (p = NS). Response to oral commands occurred at 17 and 21 min after cessation of anesthesia for sevoflurane and halothane, respectively (p = NS). No difference was seen in the incidence of postanesthesia excitement or vomiting.
27[f]	100 pediatric patients (age 6 mo–6 yr)/ myringotomy	Sevoflurane 1–7% or halothane 0.5–4.5% (both with nitrous oxide 50–70%, with and without midazolam premedication)	Time to emergence, recovery, and discharge (based on Steward scores and time in the recovery room)	Time to reach a Steward score of 6 was significantly shorter with sevoflurane than with halothane (15.9 vs. 30.8 min, $p < 0.001$). Sevoflurane was associated with a shorter time in the recovery room (21.1 vs. 35.5 min, p value not stated) and a shorter time to discharge home (50.5 vs. 57.1 min, $p = 0.046$). Patients premedicated with midazolam tended to have longer recovery times but less postoperative agitation.
28[h]	64 pediatric patients (age 44 wk–1 yr)/routine elective surgery	Halothane 3% or isoflurane 5% (both in oxygen 100%)	Time to induction (loss of eyelash reflex, tolerance of airway mask), and airway events	Time to induction was faster with isoflurane than with halothane on the basis of faster times to loss of eyelash reflex (70.1 vs. 80.2 sec, $p = 0.028$) and to tolerating the facemask (80 vs. 93.4 sec, $p = 0.0072$). No difference was seen in airway events, such as coughing, breath holding, and laryngospasm.

Continued on next page

Table 4 (*continued*)

Ref.	Patient Population/ Procedure	Anesthesia Regimen[b]	Outcome Measures	Results
29[d]	60 pediatric patients (age 3–8 yr)/elective outpatient myringotomy	Sevoflurane 1–8% or halothane 0.5–5% (both with nitrous oxide in oxygen)	Time to recovery (response to oral command [early]; excitation, pain, sitting, walking, drinking water, nausea, and discharge [intermediate])	No difference was seen in times to early or intermediate recovery for any parameter assessed. The incidence of nausea and vomiting was higher with halothane (6.7% and 6.7%) than with sevoflurane (3.3% and 0%) (p = NS).
30	48 pediatric patients (age 6 mo–13 yr)/elective surgical procedures below the umbilicus	Sevoflurane or desflurane (both with nitrous oxide in oxygen)	Airway events; arousal scores; times to spontaneous eye opening, meeting discharge criteria, and discharge	Airway events (coughing, breath holding, excessive secretions, laryngospasms, or desaturation episodes) occurred more often with desflurane than with sevoflurane (p = 0.017). No differences were seen in postextubation arousal scores, time to eye opening, time to meeting discharge criteria, or time to discharge.

[a]DSST = digit-symbol substitution test for assessment of psychomotor function, VAS = visual analog scale for mental state using subjective variables, MAC = minimum alveolar concentration, NVR = numerical verbal rating scale, NS = not significant, PACU = postanesthesia care unit, BMI = body mass index, GCS = Glasgow coma scale.
[b]Anesthesia was delivered through tracheal intubation unless otherwise noted.
[c]Aldrete scoring system assesses consciousness, activity on command, respiration, circulation, and oxygen saturation. A score of 9 or more is needed to transfer a patient to an area with less intense care.
[d]The delivery method of anesthesia was not reported.
[e]From meta-analysis.
[f]Anesthesia was delivered through laryngeal airway mask.
[g]Steward simplified scoring system assesses consciousness, airway, and movement. Using this scale, a score of 0 = fully anesthetized and 6 = fully recovered.
[h]Anesthesia was first delivered with cupped hand and then through laryngeal airway mask.

rhythmias may occur with inhaled anesthetics, most likely because of sensitization of the myocardium to catecholamines. This effect appears to be most pronounced with halothane, followed by enflurane. Sevoflurane, isoflurane, and desflurane have less potential for causing cardiac arrhythmias than do either halothane or enflurane.[2]

Neurotoxicity. Cerebral vasodilation, increased cerebral blood flow, and increased intracranial pressure (from impaired autoregulation) can result with halothane and, to a lesser degree, enflurane. The effects of desflurane, isoflurane, and sevoflurane on cerebral blood flow and intracranial pressure appear to be comparable to and less than those of either halothane or enflurane, respectively.[2]

Postoperative nausea and vomiting. Postoperative nausea and vomiting (PONV) is a common complication of surgery. Patient factors, as well as the type of surgery, can influence the occurrence of PONV; however, general inhalation anesthesia is a major contributor.[37] PONV resulting from inhaled anesthesia is usually limited to the first two hours after surgery.[38]

Sneyd et al.[39] conducted a meta-analysis of 96 clinical trials comparing propofol, an intravenous agent used for the induction and maintenance of anesthesia, with inhaled anesthetics to evaluate the rate of PONV. The median frequency of PONV with inhaled anesthetics was 25%, compared with 13% for propofol. Vomiting alone was reported in 14% of patients given inhaled anesthetics; nausea occurred in 24%.

A large, two-year, prospective trial assessing the potential for PONV with various inhaled anesthetics was conducted by Apfel et al.[38] A total of 1180 children and adults who underwent elective surgery (diagnostic procedures, adenotomy or tonsillectomy, sinus surgery, tympanoplasty, or strabismus surgery) received standard preoperative medication and

intravenous induction of anesthesia followed by an inhaled anesthetic (enflurane, isoflurane, or sevoflurane) or propofol for maintenance. The rate of PONV was the primary endpoint. The use of inhaled anesthetics was associated with an increased risk of PONV within 24 hours after surgery (47.6% with inhaled gases versus 28.8% with propofol). The odds ratios (ORs) for PONV for enflurane, isoflurane, and sevoflurane versus propofol were 3.1, 3.4, and 2.8, respectively ($p < 0.001$). During the first two hours after surgery, inhaled anesthetics were the main risk factor for PONV, with adjusted ORs of 19.8 (isoflurane), 16.1 (enflurane), and 14.5 (sevoflurane).

Respiratory effects. Respiratory depression is seen with all of the inhaled anesthetics and is dose dependent.[2] All agents produce an increase in respiratory rate, a decrease in tidal volume, and an increase in arterial carbon dioxide pressure. The muscle relaxant effects of inhaled anesthetics, resulting in bronchodilation, also contribute to respiratory depression.[40]

Respiratory irritation is related to the pungency of the agent; this effect is especially important during induction, since a highly pungent agent will result in coughing, laryngospasm, breath holding, increased secretion, and oxyhemoglobin desaturation, especially in pediatric patients.[3] Desflurane is the most pungent agent, with respiratory irritation seen above 1 MAC, while sevoflurane and halothane are generally not associated with respiratory irritation.

TerRiet et al.[41] compared isoflurane, desflurane, and sevoflurane for pungency in 81 adult patients undergoing general anesthesia for surgical procedures, with each gas inhaled at 2 MAC for 60 seconds via a laryngeal airway mask. A total of 20 patients given desflurane, 11 patients given isoflurane, and 1 patient given sevoflurane objected to inhaling the gas or coughed ($p < 0.05$). The number of patients complaining about burning, irritation, or discomfort was greatest in the desflurane group ($n = 21$), followed by patients receiving isoflurane ($n = 12$) and sevoflurane ($n = 0$) ($p < 0.05$).

Other toxicities. Malignant hyperthermia is also seen with all of the inhaled anesthetics, although halothane may have a greater potential for this effect.[2] Postanesthesia agitation, referred to as emergence agitation or emergence delirium, is characterized by severe restlessness, combativeness, disorientation, incoherence, and unresponsiveness and has been reported to occur in 12–30% of children after surgery.[42] These emergence behaviors usually last about 10 minutes, but they can last up to 45 minutes in some patients. Rapid emergence from anesthesia, as well as the use of inhaled anesthetics, is among the factors that can contribute to emergence agitation. Both desflurane and sevoflurane have been associated with a higher rate of emergence agitation than halothane.[43] Welborn et al.[25] reported a 55% rate of emergence agitation with desflurane, whereas Aono et al.[44] reported a rate of 40% among preschool boys given sevoflurane.

Drug interactions

All of the inhaled anesthetics have the potential to interact with neuromuscular blocking agents (e.g., atracurium, mivarcurium, vecuronium, cisatracurium, pancuronium), thus increasing the neuromuscular blocking agents' intensity and duration of action.[9,10,45] In addition, benzodiazepines and opioids may decrease the MAC of inhaled anesthetics. The dose of an inhaled anesthetic gas is typically adjusted and reduced when it is used in combination with nitrous oxide. In practice, these interactions become part of a "balanced anesthesia" approach, allowing for a reduced dose of some agents, such as the neuromuscular blockers, and a reduction in the MAC of the inhaled anesthetic.

Dosage and administration

Delivery systems and flow rates. Anesthetic gases are usually administered using a delivery system that mixes the anesthetic gas with carrier gases (i.e., oxygen and nitrous oxide) in varying concentrations.[1,46] The gas mixture is then fed into a rebreathing circuit that consists of an inspiratory and expiratory limb. Movement of the gas mixture within the rebreathing circuit is circular, from the inspiratory limb to the patient (inhaled gas), then from the patient to the expiratory limb (exhaled gas). Exhaled gas passes through a carbon dioxide absorber within the circuit, is remixed with fresh gas mixture, and is rebreathed by the patient. Divalent and monovalent bases (e.g., calcium, barium, sodium, and potassium hydroxides) are used as absorbents to remove carbon dioxide from the exhaled gas.[3] Some exhaled gas may be removed via an overflow valve; a reservoir bag is also attached to allow for greater variation in ventilatory flow rates.

Under certain conditions, the absorbents used to remove carbon dioxide from the gas mixture may cause the anesthetic gas to degrade into potentially nephrotoxic compounds.[3,10,35,47] Degradation may be influenced by the type of absorbent used, high temperature from both the carbon dioxide absorbent and the patient's body, and flow rate. In animal studies, absorbents such as soda lime or barium hydroxide lime, which contain sodium and potassium hydroxides (both strong bases), have been shown to result in higher concentrations of carbon monoxide and compound A than calcium hydroxide lime, potentially resulting in a greater risk of toxicity.[47]

Higher temperatures have been shown to increase the degradation of anesthetic gases; temperatures within the anesthetic delivery system are high due to the exothermic nature of the reaction between the gas and the absorbent.[3,10] The magnitude of the

temperature increase is influenced by the amount of carbon dioxide absorbed, flow rate of the gas, patient's metabolic status, and ventilation.[10] Finally, high flow rates may result in desiccation of the absorbents, thus increasing the production of degradation products of some gases.[3,35]

The flow rate may also affect the amount of anesthetic gas that escapes from the delivery system, requiring an increase in the amount of gas used and thereby raising the cost.[46] Flow rates for anesthetic delivery systems have been classified as minimal (0.25–0.5 L/min), low (0.5–1.0 L/min), medium (1.0–2.0 L/min), high (2.0–4.0 L/min), and very high (>4.0 L/min). These represent the rates at which fresh gas flows into the rebreathing delivery system. High flow rates are traditionally used, most likely to prevent accidental hypoxia and better control the depth of anesthesia. The use of low flow rates has several advantages, including a reduction in the use of the anesthetic gas and reduced release of anesthetic gas into the environment. This may be especially true for gases with low solubility, such as desflurane.[48]

Administration. The clinical effects of inhaled gases are dose dependent and result when the partial pressure of the agent in the blood reaches equilibrium with the inspired alveolar partial pressure.[8] The rate at which this equilibrium is reached is determined by the inspired concentration of the agent, ventilation, solubility of the agent in blood and tissue, cardiac output, and tissue perfusion. During surgical procedures, the dose can be controlled by observing the patient for depth of anesthesia, as well as observing the end-tidal concentrations of the agent.

Other more reliable techniques are used to determine the level of anesthesia produced with the inhaled anesthetics. One is the bispectral index monitor, which is based on a bispectral analysis of electroencephalographic signals. It incorporates electroencephalographic information on power and frequency with phase-coupling information as an indication of the depth of anesthesia.[49] The bispectral index monitor displays a number between 0 and 100, representing the depth of anesthesia. The higher the number, the lower the anesthetic level. The use of bispectral index monitoring with inhaled agents has been shown to reduce the amount of anesthetic needed, recovery and emergence times, and the rate of PONV with inhaled anesthetics.[50,51]

Inhaled gases can be used for both the induction and maintenance of anesthesia. The amount of anesthesia needed differs for each patient and depends, in part, on the presence or absence of preanesthetic medications (opioids or benzodiazepines) (Table 5).

Safety issues

One potential safety issue associated with the use of inhaled anesthetic gases is the effect of the occupational exposure of health care personnel to trace amounts of the gases.[52] Studies conducted in the 1970s concluded that female personnel exposed to trace amounts of anesthetic gases (primarily nitrous oxide) had a greater risk of spontaneous abortion, infertility, and congenital abnormalities in their children. However, subsequent review of the data revealed a lack of quality in the study design, with no quantification of exposure, lack of confirmation of the adverse outcomes reported, and no controls for confounding factors or bias. In addition, animal studies have failed to find mutagenicity, carcinogenicity, or organ toxicity with exposure to inhaled anesthetics. Teratogenicity has been demonstrated in animals after prolonged exposure during pregnancy; however, it is not clear whether this results from the agent itself or from the physiological effects that occur during anesthesia.

McGregor[52] reviewed available epidemiologic data on the safety of occupational exposure to anesthetic gases and concluded that trace amounts are not associated with adverse effects when appropriate ventilation is used and when waste gases are removed. The Occupational Safety and Health Administration has set standards for occupational exposure to inhaled anesthetic gases—<25 ppm as an eight-hour time-weighted average concentration and <2 ppm not to exceed one hour of exposure for halogenated inhaled anesthetics.[52] In addition, institutions should have a management program in place that includes the removal of waste gases, the monitoring of trace gases, practices to minimize exposure by health care personnel, and a mechanism for reporting adverse effects.[52]

Although they are rare, intraoperative fires have occurred within the delivery systems used with anesthetic gases.[10,53] The exothermic reaction between the anesthetic gas and the carbon dioxide absorbent increases as the absorbent becomes desiccated, resulting in excessive heating of the absorbent, thereby generating heat and highly flammable byproducts, such as methanol and formaldehyde. Higher temperatures may be reached with sevoflurane than with desflurane, enflurane, or isoflurane, especially when using carbon dioxide absorbents containing strong bases.

Economic issues

Drugs used for anesthesia during surgery can account for 5–13% of a hospital's drug budget.[6,54] Although various intravenous agents can be used for induction, inhaled anesthetics are the primary agents used for the maintenance of anesthesia. When selecting the most cost-effective agent, the potency, flow rate, volume of vapor produced, and amount of anesthetic gas wasted during surgery need to be considered in addition to acquisition cost. The cost per MAC hour—perhaps the best indication of the true cost of an inhaled anesthetic—can be estimated using the following formula[55]:

Cost ($) per MAC hour = (concentration × FGF × duration × MW × cost per mL) ÷ (2412 × D)

where concentration = % of gas delivered, FGF = fresh gas flow in liters per minute, duration = duration of inhaled anesthesia delivery in minutes, MW = molecular weight in grams, 2412 = factor to account for the molar volume of gas at 21 °C, and D = density in grams per milliliter.

Other methods have been used to calculate the cost of anesthetic gases. Smith[54] described a formula that used time of anesthetic delivery, fresh gas flow rate, set percentage, unit price, unit size, and milliliters of vapor produced per milliliter of liquid to calculate the cost of inhaled anesthetic per minute. The volume of vapor produced per milliliter for each of the anesthetic gases is given in Table 6, along with the average wholesale prices for the available sizes. The true acquisition price will vary considerably among institutions, since contract pricing offered by the manufacturers of the inhaled anesthetic gases is usually institution specific.

Table 5.
Administration of Inhaled Anesthetics[6,9-11]

Agent	Amount (mL/hr)[a]	Induction (%)	Maintenance (%)
Desflurane	9–76	3[b,c]	2.5–8.5
Enflurane	4–34	2.0–2.5[c]	0.5-3.0
Halothane	2–16	Variable	0.5–1.5
Isoflurane	3–24	1.5–3.0[c]	1.0–2.5
Sevoflurane[d]	15–30	NA[e]	0.5–3.0

[a]As milliliter of liquid with a goal minimum alveolar concentration of 1 and a flow rate of 0.5–4 L/min.
[b]Increased by 0.5–1% increments.
[c]Not recommended for induction because of airway irritation.
[d]At a minimum flow rate of 2 L/min.
[e]NA = not available.

Table 6.
Cost of Inhaled Anesthetics[54,56,a]

Agent	Manufacturer	AWP/Unit	AWP/ Milliliter	Volume of Vapor per Milliliter of Liquid (mL)[b]
Desflurane	Baxter	$135.44/240 mL	$0.56	209.7
Enflurane	Baxter	$110.88/250 mL	$0.44	198.5
Halothane	Hospira	$58.92/250 mL	$0.24	228.0
Isoflurane	Hospira	$42.39/100 mL	$0.42	195.7
		$130.92/250 mL	$0.52	
	Baxter	$24.00/100 mL	$0.24	
		$57.60/250 mL	$0.23	
Sevoflurane	Abbott	$269.54/250 mL	$1.08	182.7

[a]AWP = average wholesale price. AWP is used for comparison only. The cost of an anesthetic agent is best determined using the cost per MAC hour.
[b]At 20 °C and 1 atmosphere of pressure.

Therapeutic interchange

A true therapeutic interchange is likely not possible with the inhaled anesthetics. Golembiewski[57] recently presented a series of case studies highlighting patient- and product-specific factors that must be considered when selecting an anesthetic agent. Factors that may influence the efficacy or toxicity of the gas include the duration of anesthesia, surgical procedure, patient's condition (e.g., presence of hepatic or renal dysfunction, cardiac and respiratory status, weight, and age), and delivery method (e.g., laryngeal mask airway versus tracheal intubation).

Recommendations and critical issues

The inhaled anesthetics have been shown to be both safe and effective in inducing and maintaining anesthesia for surgery and other invasive procedures. These agents do, however, differ in potency, adverse-effect profile, and cost. Newer anesthetic gases, such as sevoflurane and desflurane, appear to have more favorable physicochemical properties, such as low solubility (resulting in faster uptake and elimination) and little to no metabolism. However, selection must also take into consideration patient factors, as well as the duration and type of procedure.

In practice, enflurane is generally not used in the United States because of the risk of seizures; the use of halothane is also limited because of its association with hepatotoxicity. Desflurane and sevoflurane are both attractive agents, with a faster onset of action and a shorter duration than the other inhaled agents, especially for ambulatory or minimally invasive surgeries.

References

1. Eger EI II. Current and future perspectives on inhaled anesthetics. *Pharmacotherapy.* 1998; 18:895-910.
2. Fee JP, Thompson GH. Comparative tolerability profiles of the inhaled anaesthetics. *Drug Saf.* 1997; 16:157-70.
3. Eger EI II. Characteristics of anesthetic agents used for induction and maintenance of general anesthesia. *Am J Health-Syst Pharm.* 2004; 61(suppl 4):S3-10.
4. Campagna JA, Miller KW, Forman SA. Mechanisms of actions of inhaled anesthetics. *N Engl J Med.* 2003; 348:2110-24.
5. Sonner JM, Antognini JF, Dutton RC et al. Inhaled anesthetics and immobility: mechanisms, mysteries, and minimum alveolar anesthetic concentration. *Anesth Analg.* 2003; 97:718-40.
6. Eger EI, White PF, Bogetz MS. Clinical and economic factors important to anaesthetic choice for day-case surgery. *Pharmacoeconomics.* 2000; 17:245-62.
7. Nickalls RW, Mapleson WW. Age-related iso-MAC charts for isoflurane, sevoflurane and desflurane in man. *Br J Anaesth.* 2003; 91:170-4.
8. Behne M, Wilke HJ, Harder S. Clinical pharmacokinetics of sevoflurane. *Clin Pharmacokinet.* 1999; 36:13-26.
9. Physicians' desk reference. Montvale, NJ: Thomson Healthcare; 2005.

10. Ultane (sevoflurane) package insert. North Chicago, IL: Abbott Laboratories; 2003.
11. Drug facts and comparisons. St. Louis: Facts and Comparisons; 2005.
12. Doherty TJ, Geiser DR, Frazier DL. Comparison of halothane minimum alveolar concentration and minimum effective concentration in ponies. *J Vet Pharmacol Ther.* 1997; 20:408-10.
13. Nathanson MH, Fredman B, Smith I et al. Sevoflurane versus desflurane for outpatient anesthesia: a comparison of maintenance and recovery profiles. *Anesth Analg.* 1995; 81:1186-90.
14. Philip BK, Kallar SK, Bogetz MS et al. A multicenter comparison of maintenance and recovery with sevoflurane or isoflurane for adult ambulatory anesthesia. *Anesth Analg.* 1996; 83:314-9.
15. Song D, Joshi GP, White PF. Fast-track eligibility after ambulatory anesthesia: a comparison of desflurane, sevoflurane, and propofol. *Anesth Analg.* 1998; 86: 267-73.
16. Tarazi EM, Philip BK. A comparison of recovery after sevoflurane or desflurane in ambulatory anesthesia. *J Clin Anesth.* 1998; 10:272-7.
17. Robinson BJ, Uhrich TD, Ebert TJ. A review of recovery from sevoflurane anaesthesia: comparisons with isoflurane and propofol including meta-analysis. *Acta Anaesthesiol Scand.* 1999; 43:185-90.
18. Dupont J, Tavernier B, Ghosez Y et al. Recovery after anaesthesia for pulmonary surgery: desflurane, sevoflurane and isoflurane. *Br J Anaesth.* 1999; 82:355-9.
19. Karlsen KL, Persson E, Wennberg E et al. Anaesthesia, recovery and postoperative nausea and vomiting after breast surgery. A comparison between desflurane, sevoflurane and isoflurane anaesthesia. *Acta Anaesthesiol Scand.* 2000; 44:489-93.
20. Torri G, Casati A, Albertin A et al. Randomized comparison of isoflurane and sevoflurane for laparoscopic gastric banding in morbidly obese patients. *J Clin Anesth.* 2001; 13:565-70.
21. Gauthier A, Girard F, Boudreault D et al. Sevoflurane provides faster recovery and postoperative neurological assessment than isoflurane in long-duration neurosurgical cases. *Anesth Analg.* 2002; 95: 1384-8.
22. Heavner JE, Kaye AD, Lin BK et al. Recovery of elderly patients from two or more hours of desflurane or sevoflurane anaesthesia. *Br J Anaesth.* 2003; 91: 502-6.
23. Eshima RW, Maurer A, King T et al. A comparison of airway responses during desflurane and sevoflurane administration via a laryngeal mask airway for maintenance of anesthesia. *Anesth Analg.* 2003; 96:701-5.
24. Lerman J, Davis PJ, Welborn LG et al. Induction, recovery, and safety characteristics of sevoflurane in children undergoing ambulatory surgery: a comparison with halothane. *Anesthesiology.* 1996; 84:1332-40.
25. Welborn LG, Hannallah RS, Norden JM et al. Comparison of emergence and recovery characteristics of sevoflurane, desflurane, and halothane in pediatric ambulatory patients. *Anesth Analg.* 1996; 83: 917-20.
26. Michalek-Sauberer A, Wildling E, Pusch F et al. Sevoflurane anaesthesia in paediatric patients: better than halothane? *Eur J Anaesthesiol.* 1998; 15:280-6.
27. Lapin SL, Auden SM, Goldsmith LJ et al. Effects of sevoflurane anaesthesia on recovery in children: a comparison with halothane. *Paediatr Anaesth.* 1999; 9:299-304.
28. Bagshaw ON, Stack CG. A comparison of halothane and isoflurane for gaseous induction of anaesthesia in infants. *Paediatr Anaesth.* 1999; 9:25-9.
29. Hallén J, Rawal N, Gupta A. Postoperative recovery following outpatient pediatric myringotomy: a comparison between sevoflurane and halothane. *J Clin Anesth.* 2001; 13:161-6.
30. Valley RD, Freid EB, Bailey AG et al. Tracheal extubation of deeply anesthetized pediatric patients: a comparison of desflurane and sevoflurane. *Anesth Analg.* 2003; 96:1320-4.
31. Reichle FM, Conzen PF, Peter K. Nephrotoxicity of halogenated inhalational anaesthetics: fictions and facts. *Eur Surg Res.* 2002; 34:188-95.
32. Food and Drug Administration. Schering Corp. et al.; withdrawal of approval of 51 new drug applications and 25 abbreviated new drug applications. *Fed Regist.* 2001; 66:43017-9.
33. Gentz BA, Malan TP Jr. Renal toxicity with sevoflurane: a storm in a teacup? *Drugs.* 2001; 61:2155-62.
34. Ebert TJ, Arain SR. Renal responses to low-flow desflurane, sevoflurane, and propofol in patients. *Anesthesiology.* 2000; 93:1401-6.
35. Kharasch ED, Frink EJ, Artru A et al. Long-duration low-flow sevoflurane and isoflurane effects on postoperative renal and hepatic function. *Anesth Analg.* 2001; 93:1511-20.
36. Obata R, Bito H, Ohmura M et al. The effects of prolonged low-flow sevoflurane anesthesia on renal and hepatic function. *Anesth Analg.* 2000; 91:1262-8.
37. Hough MB, Sweeney B. Postoperative nausea and vomiting in arthroscopic daycase surgery: a comparison between desflurane and isoflurane. *Anaesthesia.* 1998; 53:910-24.
38. Apfel CC, Kranke P, Katz MH et al. Volatile anaesthetics may be the main cause of early but not delayed postoperative vomiting: a randomized controlled trial of factorial design. *Br J Anaesth.* 2002; 88: 659-68.
39. Sneyd JR, Carr A, Byrom WD et al. A meta-analysis of nausea and vomiting following maintenance of anaesthesia with propofol or inhalational agents. *Eur J Anaesthesiol.* 1998; 15:433-45.
40. Dikmen Y, Eminoglu E, Salihoglu Z et al. Pulmonary mechanics during isoflurane, sevoflurane and desflurane anaesthesia. *Anaesthesia.* 2003; 58:745-8.
41. TerRiet MF, DeSouza GJ, Jacobs JS et al. Which is most pungent: isoflurane, sevoflurane or desflurane? *Br J Anaesth.* 2000; 85:305-7.
42. Manworren RC, Paulos CL, Pop R. Treating children for acute agitation in the PACU: differentiating pain and emergence delirium. *J Perianesth Nurs.* 2004; 19:183-93.
43. Moos DD. Sevoflurane and emergence behavioral changes in pediatrics. *J Perianesth Nurs.* 2005; 20:13-8.
44. Aono J, Ueda W, Mamiya K et al. Greater incidence of delirium during recovery from sevoflurane anesthesia in preschool boys. *Anesthesiology.* 1997; 87:1298-300.
45. Patel SS, Goa KL. Sevoflurane: a review of its pharmacodynamic and pharmacokinetic properties and its clinical use in general anaesthesia. *Drugs.* 1996; 51:658-700.
46. Suttner S, Boldt J. Low-flow anaesthesia: does it have potential pharmacoeconomic consequences? *Pharmacoeconomics.* 2000; 17:585-90.
47. Kharasch ED, Powers KM, Artru AA. Comparison of Amsorb, sodalime, and Baralyme degradation of volatile anesthetics and formation of carbon monoxide and Compound A in swine in vivo. *Anesthesiology.* 2002; 96:173-82.
48. Johansson A, Lundberg D, Luttropp HH. Low-flow anaesthesia with desflurane: kinetics during clinical procedures. *Eur J Anaesthesiol.* 2001; 18:499-504.
49. Bard JW. The BIS monitor: a review and technology assessment. *AANA J.* 2001; 69:477-83.
50. Joshi GP. Inhalational techniques in ambulatory anesthesia. *Anesthesiol Clin N Am.* 2003; 21:263-72.
51. Tesniere A, Servin F. Intravenous techniques in ambulatory anesthesia. *Anesthesiol Clin N Am.* 2003; 21:273-88.
52. McGregor DG. Occupational exposure to trace concentrations of waste anesthetic gases. *Mayo Clin Proc.* 2000; 75:273-7.
53. Wu J, Previte JP, Adler E et al. Spontaneous ignition, explosion, and fire with sevoflurane and barium hydroxide lime. *Anesthesiology.* 2004; 101:534-7.
54. Smith I. Cost considerations in the use of anaesthetic drugs. *Pharmacoeconomics.* 2001; 19(5, pt. 1):469-81.
55. Chernin EL. Pharmacoeconomics of inhaled anesthetic agents: considerations for the pharmacist. *Am J Health-Syst Pharm.* 2004; 61(suppl 4):S18-22.
56. Drug topics red book. Montvale, NJ: Thomson Healthcare; 2004.
57. Golembiewski J. Considerations in selecting an inhaled anesthetic agent: case studies. *Am J Health-Syst Pharm.* 2004; 61 (suppl 4):S10-7.